Association between Drinking Water Disinfection and Somatic Parameters at Birth

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We conducted an epidemiological study in Liguria, Italy, on the association between somatic parameters at birth and drinking water disinfection with chlorine dioxide and/or sodium hypochlorite. Over 2 years (1988–1989), 676 births at two public hospitals, one in Genoa (548 cases) and another in Chiavari (128 cases) were examined and data regarding both mother and child were obtained from hospital records. Results indicate a higher frequency of small body length (≤49.5 cm) and small cranial circumference (≤35 cm) in infants born to mothers who drank water treated with chlorine compounds. In particular, the statistical analysis (by simultaneous variance analysis and Scheffé test) indicated that there may be an association between infants with smaller body length and mothers who drank water treated with chlorine dioxide [adjusted odds radio (OR) = 2.0; 95% CI = 1.2–3.3] or sodium hypoclorite (adjusted OR = 2.3; 95% CI = 1.3–4.2) and between infants with smaller cranial circumference and mothers who drank water treated with chlorine dioxide (adjusted OR = 2.2; 95% CI = 1.4–3.9) or sodium hypochlorite (adjusted OR = 3.5; 95% CI = 2.1–8.5). The presence of neonatal jaundice is almost twice as likely (adjusted OR = 1.7; 95% CI = 1.1–3.1) in infants whose mothers drank water treated with chlorine dioxide. *Key words*: chlorination, chlorine dioxide, infants, pregnancy outcomes, water disinfection. *Environ Health Perspect* 104:516–520 (1996)

The presence of by-products following chlorination in drinking water (*1–8*) has in many cases encouraged the usage of chlorine dioxide. This disinfectant leads to the presence of chlorites and chlorates in the treated water, and their effects at the levels usually found in drinking water are still being investigated.

In 1982, Tuthill et al. (*9*) reported a higher rate of preterm deliveries and more weight loss at birth in Chicopee, Massachusetts, where drinking water was treated with chlorine dioxide, when compared to Holyoke, Massachusetts (not far from Chicopee), where drinking water was treated with sodium hypochlorite. Recently, Savitz et al. (*10*) conducted a population-based case–control study of miscarriage, preterm delivery, and low birth weight in Alamance, Durham, and Orange Counties in central North Carolina during the period September 1988–August 1991.

Starting with the Tuthill study (*9*) and laboratory research into the effects of chlorination on reproduction (*11–16*), we thought it would be useful to collect and analyze data to study somatic parameters of infants born to women living in areas of Genoa where municipal water is treated with sodium hypochlorite, chlorine dioxide, or both. In Genoa, the same company treats surficial and well water, using different filtration and disinfection methods.

Methods

We conducted a cross-sectional study in Genoa, Italy, on somatic parameters at birth by collecting data from hospital records at the Galliera Hospital (one of the most important in this community, located in the center of the town) covering 2 years (1988–1989). For all cases it was known whether the mothers were drinking water treated with sodium hypochlorite, chlorine dioxide, or both disinfectants. Births at the Chiavari Hospital were chosen as a control group because in this community, 30 km from Genoa, drinking water is not disinfected. Only women residing in Genoa or Chiavari were considered in this group. For 548 women in Genoa and 128 in Chiavari, we were able to verify the type (or absence) of drinking water disinfection during the pregnancy.

Genoa and Chiavari were chosen for the following reasons. Drinking water in Genoa (640,000 inhabitants) is distributed by two different water companies, one private and one public (AMGA). The public company covers the central and eastern parts of the town, which are largely residential and commercial areas. Genoa is the only town in the region of Liguria where the public water company has, for many years, simultaneously supplied both water disinfected with hypochlorite and with chlorine dioxide. Chlorine dioxide is used with rapid sand filters to treat water from the Brugneto reservoir and from the Bisagno River wells and surface water. Sodium hypochlorite is used together with Chabal sand filters for treating water from the Val Noci reservoir. One urban area of Genoa is supplied with drinking water that derives alternately from one or the other treatment plant.

The chemical characteristics of the water distributed in Genoa by the municipal plant are similar: chloride content ranges from 4.4 to 7.5 mg/l, hardness from 12.5 to 15.9°F, conductivity from 250 to 310 μSv/cm. Trihalomethanes vary from 1–3 μg/l in water treated with chlorine dioxide to 8–16 μg/l in water treated with sodium hypochlorite. Data obtained from the AMGA confirmed that during the observation period, the trihalomethane concentrations in water treated with sodium hypochlorite were always much lower than the Italian maximum permitted concentration of 30 μg/l. Chlorine residue level immediately after treatment was <0.4 mg/l, while chlorine dioxide was <0.3 mg/l.

The town of Chiavari is about 30 km east of Genoa and is smaller than Genoa (35,000 inhabitants). Chiavari, a residential center with small-scale commercial activities, is similar to the central and eastern residential areas of Genoa in terms of social and economic characteristics. The degree of industrialization is low in both areas. With regard to prenatal care, the Italian National Sanitary Service offers the same care to pregnant women in all the towns of the region (Liguria) where Genoa and Chiavari are located.

In Chiavari, the local municipal water plant uses water pumped from wells on the Entella River, without any treatment. The characteristics of drinking water in Chiavari are similar to those of the water distributed by the AMGA in Genoa: the average chloride level is 11.3 mg/l, conductivity is 319 μSv/cm, hardness is 16.6°F, and trihalomethanes are absent.

The 548 women studied in Genoa were divided into three subgroups based on the women's address and therefore on which type of disinfection was used by the municipal water plant: only chlorine dioxide, only sodium hypochlorite, or both (used alter-

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nately). This information is made available for each dwelling by the AMGA. For each birth, the following data were collected from hospital records: age of the mother, smoking, alcohol consumption, education level, preterm delivery (≤37 weeks completed gestation), cesarean section, low birth weight (≤2500 g), small body length (≤49.5 cm), a small cranial circumference (≤35 cm), and neonatal jaundice.

For each of the four subgroups of the sample under observation, statistical parameters (average values, absolute frequency, percentage of events, etc.) were calculated (Table 1–3). We used the analysis of simultaneous variance to evaluate and interpret differences in the mean values of the considered variables. When statistically significant differences were observed, more information was obtained using the multiple comparison model (Scheffè test). Figures 1–3 show averages and standard errors of variables according to mothers' age and type of drinking water disinfection.

The sample of women was divided into two groups according to level of education: those who left school upon reaching the required minimum age and those going on to higher levels. The family income level was obtained from municipal records; when this was not available, an estimate was made by comparison with subjects with the same education level.

We calculated odd ratios (ORs) by comparing exposures to the three different disinfection treatments with controls (no exposure). The ORs provide an estimate of the increased risk associated with exposure. The confidence interval indicates the statistical precision of these estimates.

On the basis of a preliminary analysis, some potential confounders were included (maternal age, education level, smoking, alcohol consumption, and sex of the child). These parameters were used to perform a logistic regression analysis (*17*) to adjust the ORs simultaneously for these confounders. Therefore, the adjusted ORs presented in Tables 4 and 5 can be interpreted as free from confounding by all the above-mentioned variables.

Table 1. Mother's age and delivery parameters

	Drinking water disinfection treatment				
	None *n* (%)	Chlorine dioxide *n* (%)	Sodium hypochlorite *n* (%)	Chlorine dioxide and sodium hypochlorite *n* (%)	Total *n* (%)
Mother's age					
≤30 years	74 (11.0)	158 (23.3)	63 (9.3)	96 (14.2)	391 (57.8)
>30 years	54 (8.0)	119 (17.6)	45 (6.6)	67 (10.0)	285 (42.2)
Total	128 (19.0)	277 (40.9)	108 (15.9)	163 (24.2)	676 (100)
Length of pregnancy					
>37 weeks	122 (18.2)	251 (37.4)	100 (14.9)	148 (22.0)	621 (92.5)
≤37 weeks (preterm)	6 (0.9)	24 (3.6)	6 (0.9)	14 (2.1)	50 (7.5)
Total	128 (19.1)	275 (41.0)	106 (15.8)	162 (24.1)	671 (100)
Delivery					
Normal	99 (14.7)	211 (31.2)	92 (13.6)	133 (19.7)	535 (79.2)
Cesarean section	29 (4.3)	66 (9.7)	16 (2.4)	30 (4.4)	141 (20.8)
Total	128 (19.0)	277 (40.9)	108 (16.0)	163 (24.1)	676 (100)

Table 2. Somatic parameters at birth

	Drinking water disinfection treatment				
	None *n* (%)	Chlorine dioxide *n* (%)	Sodium hypochlorite *n* (%)	Chlorine dioxide and sodium hypochlorite *n* (%)	Total *n* (%)
Sex					
Male	59 (8.7)	143 (21.2)	58 (8.6)	81 (12.0)	341 (50.5)
Female	69 (10.2)	134 (19.8)	50 (7.4)	82 (12.1)	335 (49.5)
Total	128 (18.9)	277 (41.0)	108 (16.0)	163 (24.1)	676 (100)
Birthweight					
≤2500 g	1 (0.2)	10 (1.6)	2 (0.3)	7 (1.2)	20 (3.3)
>2500 g	127 (20.6)	239 (38.7)	89 (14.4)	142 (23.0)	597 (96.7)
Total	128 (20.8)	249 (40.3)	91 (14.7)	149 (24.2)	617 (100)
Body length					
≤49.5 cm	55 (10.5)	120 (22.9)	52 (9.9)	61 (11.6)	288 (54.9)
>49.5 cm	70 (13.3)	82 (15.6)	29 (5.5)	56 (10.7)	237 (45.1)
Total	125 (23.8)	202 (38.5)	81 (15.4)	117 (22.3)	525 (100)
Cranial circumference					
≤35 cm	71 (13.5)	144 (27.5)	67 (12.8)	88 (16.8)	370 (70.6)
>35 cm	54 (10.3)	56 (10.7)	15 (2.9)	29 (5.5)	154 (29.4)
Total	125 (23.8)	200 (38.2)	82 (15.7)	117 (22.3)	524 (100)
Neonatal jaundice					
Absent	109 (16.1)	211 (31.2)	85 (12.6)	138 (20.4)	543 (80.3)
Present	19 (2.8)	66 (9.8)	23 (3.4)	25 (3.7)	133 (19.7)
Total	128 (18.9)	277 (41.0)	108 (16.0)	163 (24.1)	676 (100)

Results

Our results showed that the average birthweight of children was higher ($p<0.0001$) when mothers were older than 30 years of age and did not consume water disinfected with chlorine; the same was not true for younger mothers (Fig. 1). Similar observations (Figs. 2 and 3) can be drawn from data about the body length and cranial circumference, which was significantly smaller only for the children of mothers older than 30 who consumed water disinfected either with chlorine dioxide (body length, $p = 0.005$; cranial circumference, $p = 0.022$) or sodium hypochlorite (body length, $p = 0.003$; cranial circumference, $p = 0.0001$). Average cranial circumference was also smaller when both disinfectants were used ($p = 0.0003$).

For the different variables considered in this study, the crude and adjusted ORs were calculated by comparing exposures to disinfection treatments with no exposure. (Tables 4 and 5). With regard to preterm delivery (≤37 weeks completed gestation), cesarean section, and birthweight ≤2500 g, the adjusted ORs did not indicate a significant association with exposure to disinfection with chlorine compounds. On the other hand, body length ≤49.5 cm was almost twice as frequent when mothers drank water disinfected with chlorine dioxide (adjusted OR = 2.0; $p<0.01$) or with sodium hypochlorite (adjusted OR = 2.3; $p<0.01$).

The risk of a cranial circumference ≤35 cm was twice as high with exposure to chlorine dioxide (adjusted OR = 2.2; $p<0.005$) and more than tripled when the mother drank water disinfected with sodium hypochlorite (adjusted OR = 3.5; $p<0.001$). When mothers were exposed to both water disinfectants, the risk was intermediate between the two (adjusted OR = 2.4; $p<0.001$).

The frequency of neonatal jaundice almost doubled with exposure to chlorine dioxide-treated water (adjusted OR = 1.7; $p<0.05$), but it was not influenced by other types of drinking water disinfection.

Discussion

The disinfection of drinking water with chlorine dioxide results in the presence of chlorites and chlorates in the water. Chlorites oxidize hemoglobin to methemoglobin in rats (*in vitro* and *in vivo*) and in humans (*in vitro*) (*18,19*). Moreover, they produce hydrogen peroxide *in vivo*, with consequent hemolysis in animals (rats and cats) at levels too low to provoke methemoglobin.

Fetuses and newborn infants are more sensitive than adults to oxidative stress, and their blood cells may be damaged (*20*). The potential effects of chlorite on human newborns may be increased because infants consume nearly three times as much liquid per unit body weight as adults (*21*). Fetal hemoglobin is more readily oxidizible than adult hemoglobin, and infants have a lower enzymatic capacity to reduce methemoglobin once it is formed (*9*). Infants also have a shortage of antioxidants such as vitamin E (*22*), and for these reasons they are considered at high risk to the effects of drinking water disinfected with chlorine dioxide.

Couri et al. (*23*) studied the embryotoxic effects of chlorine dioxide via different exposure routes (water, food, and injection into the peritoneal cavity) in pregnant female rats. They observed an increase in intrauterine deaths, smaller litter size, and smaller offspring body weight. These effects are associated with hypoxia, which is a consequence of methemoglobinemia and hemolysis.

Heffernan et al. (*18*) reported reduction of glutathione levels in red blood cells incubated with ClO_2^-. Abdel-Rahman et al. (*24*) confirmed these results with

Table 3. Mother's age and somatic parameters at birth according to drinking water disinfection treatment

	Drinking water disinfection treatment				
	None	Chlorine dioxide	Sodium hypochlorite	Chlorine dioxide and sodium hypochlorite	Total
Mother's age (years)					
n	128	277	108	163	676
Median	30	30	29	30	30
Median absolute deviation	3	3	3	3	3
Length of pregnancy (weeks)					
n	128	275	106	162	671
Median	40	40	40	39	40
Median absolute deviation	1	1	1	1	1
Birthweight (g)					
n	128	249	91	149	617
Mean	3421.44	3185.18	3132.08	3176.71	3224.32
95% CI	3340.87–3502.01	3133.04–3237.32	3055.53–3208.64	3111.72–3241.70	3190.50–3258.14
Body length (cm)					
n	125	202	81	117	525
Mean	49.85	49.18	49.19	49.92	49.40
95% CI	49.50–50.19	48.93–49.43	48.85–49.55	49.10–49.74	49.24–49.55
Cranial circumference (cm)					
n	125	200	82	117	524
Mean	35.23	34.82	34.14	34.41	34.72
(95% CI)	34.98–35.48	34.52–35.13	33.86–34.42	34.18–34.63	34.57–34.87

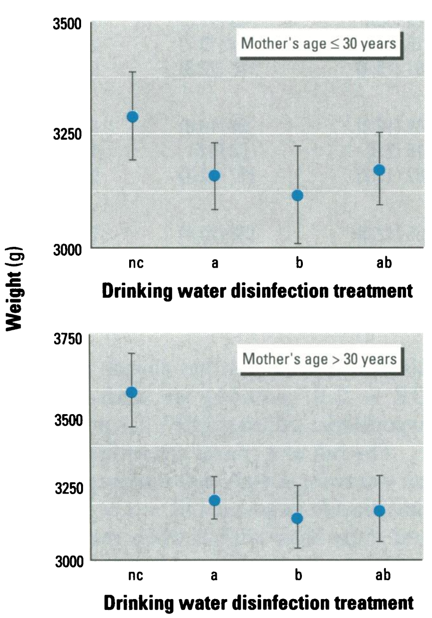

Figure 1. Birthweight (mean and 95% CI) of newborn infants of mothers over and under 30 years of age, according to drinking water disinfection. nc, no treatment; a, chlorine dioxide; b, sodium hypochlorite; ab, chlorine dioxide and sodium hypochlorite. Mother's age ≤30 years, no significant differences; mother's age >30 years, nc vs. a, $p < 0.0001$; nc vs. b, $p < 0.0001$; nc vs. ab, $p < 0.0001$ (Scheffé test).

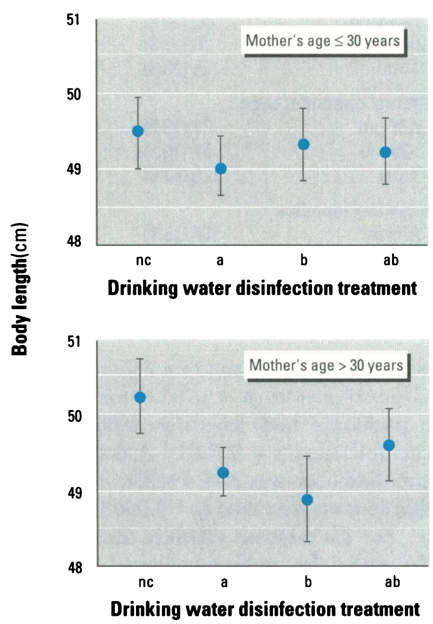

Figure 2. Body length (mean and 95% CI) of newborn infants of mothers over and under 30 years of age, according to drinking water disinfection. nc, no treatment; a, chlorine dioxide; b, sodium hypochlorite; ab, chlorine dioxide and sodium hypochlorite. Mother's age ≤30 years, no significant differences; mother's age >30 years, nc vs. a, $p < 0.005$; nc vs. b, $p < 0.003$; nc vs. ab, nonsignificant (Scheffé test).

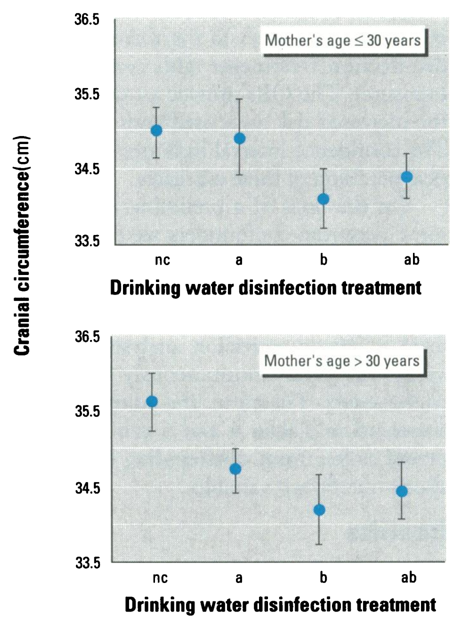

Figure 3. Cranial circumference (mean and 95% CI) of newborn infants of mothers over and under 30 years of age, according to drinking water disinfection. nc, no treatment; a, chlorine dioxide; b, sodium hypochlorite; ab, chlorine dioxide and sodium hypochlorite. Mother's age ≤30 years, no significant differences; mother's age >30 years, nc vs. a, $p = 0.022$; nc vs. b, $p = 0.0001$; nc vs. ab, $p = 0.0003$ (Scheffé test).

ClO_2^- and extended the observation to ClO_2 and ClO_3^- (*24*). A thyroid-inhibiting effect of chlorine dioxide in monkeys has also been described (*25*). Taylor and Pfohl (*26*) attributed this effect to the reduction in brain growth they observed in neonatal rats.

The results of the above-mentioned studies, carried out at high exposure levels in animals, indicate that consumption of drinking water treated with chlorine dioxide may be associated with adverse effects on the hemopoietic system and also with embryotoxicity (alterations of fetal development and neonatal growth).

Only limited research results are available on the outcomes we studied (*12*). Kramer et al. (*27*) associated exposure to chloroform concentrations above 10 ppb in drinking water with a small increase in the risk of low birthweight (adjusted OR = 1.3) and a somewhat greater risk of small-for-gestational-age (SGA) births (adjusted OR = 1.8). Using birth and fetal death certificates to identify birthweight, preterm delivery, SGA, and fetal deaths, a study was conducted in northern New Jersey (*28*): mean birthweight was reduced slightly in relation to the use of surface water supplies and in relation to the use of water with trihalomethane concentrations >100 ppb (adjusted OR = 1.1–1.4).

Savitz et al. (*10*) evaluated the risk associated with water sources, water consumption, and trihalomethane concentrations in a case–control study of miscarriage, preterm delivery, and low birthweight in central North Carolina. Water source and trihalomethane concentrations were not related to any of these pregnancy outcomes but an increase in the amount of water ingested was associated with decreased risks of all three outcomes.

In our study we observed a significant difference in some somatic parameters of newborn infants. Although this effect can be explained in light of the results of animal studies (*23–26*), it is more difficult to understand why the differences were significant only in infants born to mothers of more than 30 years old. It is noteworthy that another study in Liguria (*29*) showed that somatic parameters of the newborn child are not affected by several factors, including birthplace, socioeconomic and cultural background, and number of pregnancies. A plausible hypothesis may be that the defense and/or adaptative processes against oxidant stress are deteriorated in women who have been drinking water treated with chlorine dioxide over a longer period of time and therefore the effects on the fetus during pregnancy are more relevant.

We also observed that infants of women who consumed drinking water treated with chlorine compounds during pregnancy were at higher risk (adjusted) for some outcomes, such as body length ≤49.5 cm, cranial circumference ≤35 cm, and neonatal jaundice. It is necessary to emphasize that associations resulting from our data must be considered carefully because the quantity of water consumed during pregnancy was not considered and we ignored nutritional habits, amount of smoking, and age distribution of the women.

In conclusion, our study provides some new information on the possible association between some drinking water disinfection treatments and somatic parameters of infants at birth. Further investigations will be needed to verify the results of the present study by rigorous exposure assessment.

Table 4. Estimates of the relative risk in relation to drinking water disinfection systems

Water treatment			Crude OR	Adjusted OR[b]	95% CI
Length of pregnancy[a]	≤37 weeks	>37 weeks			
None	6	122	1.0	1.0	—
Chlorine dioxide	24	251	1.9	1.8	0.7–4.7
Sodium hypochlorite	6	100	1.2	1.1	0.3–3.7
Both	14	148	1.9	1.8	0.6–5.0
Delivery	Cesarean section	Normal			
None	29	99	1.0	1.0	—
Chlorine dioxide	66	211	1.1	1.0	0.6–1.8
Sodium hypochlorite	16	92	0.6	0.6	0.3–1.2
Both	30	133	0.8	0.8	0.4–1.5
Neonatal jaundice	Present	Absent			
None	19	109	1.0	1.0	
Chlorine dioxide	66	211	1.8	1.7	1.1–3.1*
Sodium hypochlorite	23	85	1.6	1.1	0.7–2.8
Both	25	138	0.9	0.8	0.6–1.6

OR, odds ratio.
[a]Normal is >37 weeks; ≤ 37 weeks is preterm.
[b]Adjusted according to education level, income, mother's age, smoking habit, and sex of child.
*p <0.05.

Table 5. Estimates of the relative risk in relation to drinking water disinfection systems

Water treatment			Crude OR	Adjusted OR[a]	95% CI
Weight	≤2500 g	>2500 g			
None	1	127	1.0	1.0	—
Chlorine dioxide	10	239	5.3	5.9	0.8–14.9
Sodium hypochlorite	2	89	2.9	6.0	0.6–12.6
Both	7	142	6.3	6.6	0.9–14.6
Body length	≤49.5 cm	>49.5 cm			
None	55	70	1.0	1.0	—
Chlorine dioxide	120	82	1.9	2.0	1.2–3.3*
Sodium hypochlorite	52	29	2.3	2.3	1.3–4.2*
Both	61	56	1.4	1.4	0.8–2.5
Cranial circumference	≤35 cm	>35 cm			
None	71	54	1.0	1.0	—
Chlorine dioxide	144	56	2.0	2.2	1.4–3.9**
Sodium hypochlorite	67	15	3.4	3.5	2.1–8.5†
Both	88	29	2.3	2.4	1.6–5.3†

OR, odds ratio.
[a]Adjusted according to education level, income, mother's age, smoking habit, and sex of child.
*p <0.01; **p <0.005; †p <0.001.

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